A small molecule inhibitor of redox-regulated protein translocation into mitochondria.

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Public Summary:
The mitochondrial disulfide relay system of Mia40 and Erv1/ALR facilitates import of the small translocase of the inner membrane (Tim) proteins and cysteine-rich proteins. A chemical screen identified small molecules that inhibit Erv1 oxidase activity, thereby facilitating dissection of the disulfide relay system in yeast and vertebrate mitochondria. One molecule, mitochondrial protein import blockers from the Carla Koehler laboratory (MitoBloCK-6), attenuated the import of Erv1 substrates into yeast mitochondria and inhibited oxidation of Tim13 and Cmc1 in in vitro reconstitution assays. In addition, MitoBloCK-6 revealed an unexpected role for Erv1 in the carrier import pathway, namely transferring substrates from the translocase of the outer membrane complex onto the small Tim complexes. Cardiac development was impaired in MitoBloCK-6-exposed zebrafish embryos. Finally, MitoBloCK-6 induced apoptosis via cytochrome c release in human embryonic stem cells (hESCs) but not in differentiated cells, suggesting an important role for ALR in hESC homeostasis.

Scientific Abstract:
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